UNITED STATES DEPARTMENT OF COMMERCE
Pat nt and Trademark Offic
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

ID

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/458,366	12/09/99	EVANS R	SALK2270-2

HM22/0227

Stephen E. Reiter
Gray Cary Ware & Freidenrich LLP
4365 EXECUTIVE DRIVE
SUITE 1600
SAN DIEGO CA 92121-2189

EXAMINER	
WOITACH, J	
ART UNIT	**PAPER NUMBER**
1632	17

DATE MAILED: 02/27/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File

Office Action Summary	Application No. 09/458,366	Applicant(s) Evans, R. M.
	Examiner Joseph Woitach	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Dec 11, 2000*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *13-38* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *13-38* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

File

DETAILED ACTION

The amendment filed December 11, 2000, paper number 14 has been received and entered. Claims 6, 8, and 10-13 have been canceled. Claims 13-38 have been added. Claims 13-38 are pending and currently under examination.

This application is a continuation in part of 09/227,718, filed 1/8/99, which is a continuation in part of application 09/005,286, filed 1/9/98.

Information Disclosure Statement

The references for the supplemental IDS has been received and entered, however a supplemental form PTO-1449 was not been received. While a PTO-1449 is not being sent with this action, it is noted that the three references (WO 99/48915, WO 99/61622 and WO 99/19354) have been reviewed and considered.

Specification

The sequence listing and CFR disk have been received and entered, paper numbers 15 and 16, however it is noted that the specification contains a nucleotide sequence of six base pairs which is not defined with a SEQ ID NO: (page 9, line 11, the half site is not defined by a SEQ ID NO, page 56; line 8, the Kozak sequence).

Therefore, the objection to the disclosure stands because of the following informalities: The specification contains nucleotide sequences not recited in the sequence listings. The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

Appropriate correction is required.

For a complete response to this office action, applicant must submit the required material for sequence compliance.

Claim Objections

Claims 14-34 and 36-38 are objected to because of the following informalities: Claims 14-34 and 36-38 are dependent on claims 13 and 35, respectively, however each claim recites '**A** transgenic mouse according to' or '**A** method according to'. Since the claims are dependent they should indicate their antecedent basis and recite '**The** transgenic mouse' or '**The** method'. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 6 and 8 rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is withdrawn. Claims 6 and 8 have been canceled rendering the basis of the rejection moot. It is noted that newly added claims 13-38 are recite and are directed only to a transgenic mouse.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 13-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date

sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

The specification provides adequate written description for a transgenic mouse whose genome comprises a transgene operably linked to the albumin promoter/enhancer which encodes a human steroid and xenobiotic receptor (SXR) polypeptide as set forth in SEQ ID NO: 2, and a transgene operably linked to the albumin promoter/enhancer which encodes a fusion protein comprising the activation domain of VP16 from herpes simplex virus and the amino terminal of SXR (VPSXR), however the specification fails to describe the other species of 'SXR polypeptides' within the genus of polypeptides expressed in a transgenic mouse under any promoter, and consequently the genus of transgenic mice encompassed in the claims with particularity to indicate that Applicants had possession of the claimed invention. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case,

the claimed embodiments of a transgenic mouse encoding 'a SXR polypeptide operably linked to an inducible promoter/enhancer' or to 'a SXR polypeptide operably linked to a constitutively active promoter/enhancer', lack a written description. The specification fails in two parts, first to describe adequately what is encompassed by a 'SXR polypeptide' and secondly, to describe molecular or morphological phenotypes which would be associated with expression and presence of a 'SXR polypeptide' in any tissue besides the liver. First, the specification describes the isolation and characterization of a single polynucleotide encoding a human SXR as set forth in SEQ ID NO: 2. By homology comparisons the encoded polypeptide belongs to a large nuclear receptor superfamily which share structural similarities but vary greatly in expression patterns and biological activities. While the specification indicates that the SXR set forth in SEQ ID NO: 2 may be part of a orphan family of receptors (page 9; lines 5-21), there is no indication in the specification that a 'SXR polypeptide' would encompass fusion proteins with domains of other steroid receptors or other transcription factors. The specification describes and defines in part the differences between SXR and other steroid receptors functionally, however the only example of another 'SXR polypeptide' is the VPSXR fusion protein which is not sensitive or inducible like the SXR polypeptide and therefore as functionally described would not be considered by one of ordinary skill in the art to be a SXR polypeptide. Secondly, the specification only describes the expression of the transgene operably linked to the albumin promoter/enhancer and consequential phenotype of the expression in the liver for the human SXR polypeptide and the VPSXR polypeptide. The specification does not specifically teach other inducible or constitutive

promoters/enhancers nor the phenotypic consequence to the transgenic mouse of expressing the transgene under the regulation of a promoter/enhancer other than the albumin promoter/enhancer. In addition the claims encompass expression in the intestine, however the sole example provided in the specification clearly teach that there was no detectable expression in the intestine (page 62; lines 20-25). In light of the intended breadth encompassed by a 'SXR polypeptide' and the intended expression under essentially any promoter, the skilled artisan cannot envision all the possible phenotypes which may occur due to transgene expression, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, for a transgenic mouse whose genome comprises a transgene operably linked to the albumin promoter/enhancer which encodes a human steroid and xenobiotic receptor (SXR) polypeptide as set forth in SEQ ID NO: 2, and a transgene operably linked to the albumin promoter/enhancer which encodes a fusion protein comprising the activation domain of VP16 from herpes simplex virus and the amino terminal of SXR (VPSXR) meets the written description

provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 13-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for two transgenic mice: first, a transgenic mouse whose genome comprises a transgene operably linked to the albumin promoter/enhancer, wherein said transgene comprises a polynucleotide sequence which encodes a human steroid and xenobiotic receptor (SXR) polypeptide set forth in SEQ ID NO: 2, wherein said SXR polypeptide; i) forms a heterodiamer with retinoid X receptor, ii) binds to a direct or inverted repeat element comprising the half site RGBNNM, wherein: R is selected from A or G; B is selected from G, C, or T; each N is independently selected from A, T, C, or G; and M is selected from A or C; with the proviso that at least 4 nucleotides of said RGBNNM sequence are identical with the nucleotides at corresponding positions of the sequence AGTTCA; and iii) activates transcription of steroid inducible P450 genes in response to a variety of natural and synthetic steroid hormones; wherein said mouse expresses said transgene in the liver, and wherein expression of said transgene encoding the SXR polypeptide results in the ability of the transgenic mouse upon administration of steroids and xenobiotics to increase transcription of P450 genes which are not increased in the wild type littermates treated in the same manner; and second, a transgenic mouse whose genome comprises a transgene, wherein said transgene comprises; a) a transgene which encodes a fusion

protein comprising the VP16 activation domain of the herpes simplex virus and the amino terminal of SXR, wherein said fusion protein is an activated form of human steroid and xenobiotic receptor polypeptide (VPSXR), and said fusion protein is characterized by; i) forming a heterodiamer with retinoid X receptor, ii) binds to a direct or inverted repeat element comprising the half site RGBNNM, wherein: R is selected from A or G; B is selected from G, C, or T; each N is independently selected from A, T, C, or G; and M is selected from A or C; with the proviso that at least 4 nucleotides of said RGBNNM sequence are identical with the nucleotides at corresponding positions of the sequence AGTTCA, and iii) constitutively activates transcription through response elements found in steroid inducible P450 genes; and b) wherein said gene is operably linked to the albumin promoter/enhancer, wherein said mouse expresses said gene encoding VPSXR in the liver, and wherein expression of said gene encoding VPSXR results in growth retardation and hepatomegaly in said mouse; does not reasonably provide enablement for a transgenic mouse expressing comprising a polynucleotide encoding a SXR polypeptide other than that set forth in SEQ ID NO: 2 or a VPSXR polypeptide operably linked to any inducible promoter/enhancer or expressed in any other tissue than the liver. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

Applicants argue that new claims 13-38 as written fully satisfy the requirements of 35 USC 112, first paragraph. Applicants argue that the new claims require that the transgenic animal

have a genome that contains a transgene comprising a gene encoding a human steroid and xenobiotic receptor (SXR) polypeptide operably linked to an inducible or constitutively active promoter/enhancer, and that said polypeptide is detectably expressed in the liver and the intestine. See applicants amendment page 10, third full paragraph. Further, Applicants correctly indicate that Examiner has pointed out that the specification provides enablement for two transgenic mice (previous office action, paper number 9, pages 3-4). It is also noted that newly added claims recite and encompass only a transgenic mouse. Applicants arguments have been fully considered but not found persuasive.

The claims are broad, encompassing generation a transgenic mouse wherein the expression of a 'SXR polypeptide' is controlled by essentially any promoter/enhancer, and as the claim is written, any polypeptide which maintains one of the characterizations recited in the claims. Dependent claims 14 and 25 recite specific phenotypes exhibited by the transgenic mouse, however the independent claims and most of the remaining claims which are dependent on the independent claims simply require that the transgene be expressed. With respect to claim 23, any gene encoding 'an endogenous SXR polypeptide' can be disrupted.

As discussed in the previous office action and *supra*, the specification teaches specifically how to create the two mice recited in the basis of the rejection. However, the specification is silent with respect to guidance or example for the creation of transgenic mouse in the full breadth of the claim. There is no guidance, nor art of record teaching any other SXR polynucleotide sequence beside the one set forth in the specification, teaching other specific inducible or

constitutively active promoters/enhancers other than the albumin promoter/enhancer, the use of other promoters for expression of a transgene in tissue other than liver, nor is there specific guidance for the use of appropriate vectors for the creation of transgenic and knock-out mice. In addition to the intended breadth and biological activities encompassed with a 'SXR polypeptide' as discussed above in the written description rejection, the specification is silent with respect to whether the human SXR polypeptide taught in the specification will work in all tissues at any expression level, or guidance on how one would define and obtain an operable homologue from another species other than the human SXR. In addition, no SXR gene sequence is disclosed, only the cDNA sequence of one family member, and so the specification is silent with respect to specific guidance on how one would isolate or create a transgenic mouse which comprises a homozygous disruption in any SXR gene which encodes a SXR polypeptide.

As discussed in the previous office action, as reviewed in Evans, steroid receptors are part of a large superfamily of receptors which are activated by the binding of a steroid or in some case xenobiotic agents wherein the binding results in binding of promoter elements and activation of gene transcription (page 891; figure 2). The complex physiology of these molecules is reviewed by Beato *et al.* who conclude that 'recent developments shows that the controls of gene expression by steroid hormones is far more complex that was apparent at the time when the genes for SHRs were isolated. With more and more players getting on stage, we realize not only this complexity but also the persuasive role steroid hormones play in a vast number of physiological and pathological precesses' (pages 855-6; bridging paragraph). Manglelsdorf *et al.* described the

nuclear superfamily as over 150 different proteins with a complex array of extracellular signals and transcriptional responses (page 841; first paragraph). While the reviews mean to stress the commonalities among various signaling pathways, they clearly indicates the complexity involved in the activity of the various family members. Manglelsdorf *et al.* summarizes the state of the art commenting that 'it is possible to consider each receptor or each hormone in isolation and to extract common themes, body physiology is rarely so simple' (page 847; bottom of column 2) however concludes that while 'the advances of the last 10 years can be viewed with satisfaction, there is still a long and challenging journey ahead' (page 848; final line). Essentially, at the time of filing of the present application, RXRs represented a growing number of superfamily members with increasingly more complex function, particularly when extended to *in vivo* physiology. The present application has defined a novel member of the SXR family of receptors and defined some of functions *in vitro* cell culture systems and *in vivo* using transgenic mice, however, the specification of the present application, nor the art of record, has resolved the many complexities of the role of this receptor in all animals, nor has it resolved the role of this molecule for use in full the scope recited in the claims.

The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). This is particularly true in the art of transgenic animals with respect to transgene behavior. Without evidence to the contrary, transgene expression in different species of transgenic animals is not consistent and varies according to the particular host species. This observation is specifically supported by Hammer *et al.* report the production of transgenic mice, sheep and pigs;

however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The observation is further supported by Mullins *et al.* who report on transgenesis in the rat and larger mammals. Mullins *et al.* state that "a given construct may react very differently from one species to another" (page S39, Summary). Wall *et al.* further report that "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies" (page 2215, first paragraph). Since the applicants have not disclosed all the nucleic acids encompassed by the claims, there is no way to predict efficiency nor expression of a transgene.

With regard to claim 23, the specification is silent on how to obtain a transgenic mouse with a disruption in **an** endogenous SXR gene. There are no gene sequences disclosed in the specification which would be necessary for the construction of a SXR knock-out mouse. Further, there is no indication that another SXR family member exists. Finally, even if one of ordinary skill in the art had the proper gene sequences and created the appropriate vectors and ES cells, it is not clear that such knock-out mice could be created because of the general importance and complexity of RXRs in development and the normal physiology of the animal (reviewed in Beato *et al.* and Evans). The specification is silent with respect to guidance or example on how to create or identify the animal recited in claim 23. The transgenic animal in claim 23 is prophetic, besides the technical limitations of creating a transgenic mouse which has a desired SXR gene disrupted, the complexities identified for the creation of the transgenic animal apply to the

creation of a transgenic animal which does not express a SXR polypeptide. In particular, because of the importance of RXR superfamily members it is not clear that The lack of examples and specific guidance in the present application do not serve as a nexus between the complex role of RXR and the ability to express as transgenes or knock-out these molecules in all animals.

Applicants have described a prophetic transgenic animal wherein any animal would be used to express a receptor polypeptide encompassing the recited embodiments of the claim. While the methodology to create transgenic mice is routine, the creation of any transgenic animal is not. In particular, no ES cell for animals other than mice exists to date, so the creation of animals which depend on homologous recombination are not enabled in the art. Further, while methods for the introduction of a gene are routine, the expression of the gene and resulting phenotype of the animal is not. Without an actual reduction to practice, it is possible to predict that introduction of a transgene or an alteration to a gene would result a predictable phenotype or even in a viable animal.

In view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would have required undue experimentation by one of skill to practice the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claims 13-16, 21, 24-27 and 35 are vague and unclear in the recitation of 'encoding a human steroid and xenobiotic receptor (SXR) polypeptide' because it is not clear what is encompassed by a SXR polypeptide. Applicants have identified a cDNA encoding a SXR polypeptide as set forth in SEQ ID NO: 2, and defined the SXR functionally in the specification (page 17; lines 8-18), however the broad functional language used to describe the SXR polypeptide encompasses many other types of RXR heterodiamers as discussed in Mangelsdorf *et al.* (Cell 83:841-850) and it is unclear if these polypeptides are also encompassed by the claims. Further, dependent claims indicate the SXR polypeptide encompasses fusion proteins comprising combining the DNA binding domain and the activation domains of various transcriptional factors (for example claims 15, 21 and 26). The specification only defines one functional fusion protein which is constitutively active not 'unteachably active' as required for a SXR polypeptide and recited in claim 13. The claims are indefinite because one of ordinary skill in the art would not know the metes and bounds of all the other possible combinations of DNA binding domains and activation domains which would meet the limitations recited in the claims and encompassed by 'a SXR polypeptide'.

Claim 13 is unclear in the recitation of 'in response to a wide variety of natural and synthetic steroid hormones, including at least compounds that induce catabolic enzymes, ... and

bioactive dietary compounds' because many of the compounds that induce transcription are not steroid hormones. It is not clear if what is encompassed is only steroid hormones which bind and activate the SXR polypeptide or other compounds which activates transcription but through less direct signaling routes.

Claim 13 is unclear and vague in the recitation of 'linked to an inducible promoter/enhancer' because the final line of the claim recites that the SXR polypeptide is expressed 'in at least one of the liver and intestine'. The link between inducible promoter/enhancer and the expression in the liver and intestine is not apparent, and it is unclear if the ineducability is only in the liver and/or intestine or in other tissues including at least the liver and/or intestine. Further, as written it is not clear if the inducible promoter refers to the polypetide or the transgene.

Claims 14, 23 and 36 are vague and unclear in the recitation of 'a response' because an expected response to a steroid hormone is not clearly defined in the specification. The claims are indefinite because one of ordinary skill in the art would not know what the metes and bounds of what is encompassed by a response.

Claim 16 is unclear in the recitation of 'the ligand binding domain and DNA binding domain' because it does not have antecedent basis in claim 13.

Claim 23 is vague, unclear and indefinite in the recitation of 'a homozygous disruption' because the type of disruption encompassed by the claim is unclear. Further, it is unclear what the metes and bounds of a 'decreased response' are. Many types of genetic disruptions are possible

and also there are many possible functions attributed to the SXR polypeptide, and thus it is unclear if a complete absence of activity is encompassed by the claim or if only a decrease in certain specific SXR activities.

Claim 23 is unclear in the recitation of '**an** endogenous SXR polypeptide gene' because the specification has only defined one sequence encoding the endogenous SXR polypeptide set forth in SEQ ID NO: 2, and it is not clear if other SXR genes exist beyond the one which encodes SEQ ID NO: 2 or if other genes exist, that disrupting these genes would result in a change in response to steroids as compared to wild-type mice.

Claim 24 is unclear and vague in the recitation of 'linked to a constitutively active promoter/enhancer' because the final line of the claim recites that the SXR polypeptide is expressed 'in at least one of the liver and intestine'. The link between constitutively active promoter/enhancer and the expression in the liver and intestine is not apparent, and it is unclear if the promoter is active only in the liver and/or intestine or in other tissues including at least the liver and/or intestine. Further, as written it is not clear if the constitutively active promoter refers to the polypetide or the transgene.

Claim 25 is unclear because expression the SXR polypeptide only in the liver, not the intestine as recited in dependent claim 24, would result in growth retardation and hepatomegaly.

Claims 26 and 27 are unclear because an SXR polypeptide necessarily comprises a SXR ligand binding domain and a DNA binding domain obtained from a transcription activating factor, in particular from SXR.

Claim 28 is vague and unclear in the recitation of 'is further transformed with a vector' because it is not clear if the vector is present as another transgene or if the vector is introduced only to certain cells/tissues in the transgenic mouse. Further, it is unclear how the recited elements of the vector are operably linked. As recited a transgenic mouse containing in its genome the vector comprising a CMV promoter constitutively expressing any transgene wherein any hormone response element is present would anticipate this portion of the claim. It is unclear if the hormone response element is the same as that defined in the direct or inverted repeat element defined in dependent claim 24.

Claim 31 is vague, unclear and indefinite in the recitation 'the response element in the reporter vector is based on' because the metes and bounds of what is encompassed by 'based on' is unclear and thus indefinite. A response element comprising the recited half site and various variations is clear and definite, however an element based on the recited sequence is unclear because one would not know how many changes or how different the sequence could become and still be considered that it is based on the half site.

Claim 35 is incomplete because it is a method claim for producing a transgenic mouse however the final step results only in a zygote. Further, the claim only recites that the mouse expresses the SXR polypeptide in the liver and there is no indication that the transgene is incorporated into the genome to create a transgenic mouse.

Conclusion

No claim is allowed. Claims 13-38 are free of the art of record because the prior art of record fails to teach or suggest the human SXR polynucleotide or polypeptide as set forth in the specific SEQ IDs with the specific biological activities set forth in the independent claims. Further, the SXR is a member of an orphan receptor family and the art fails to specifically teach or suggest the biological activities of the encoded polypeptide or the resulting phenotypes when expressed under the albumin promoter/enhancer in transgenic mice. However, these claims are subject to other rejections.

Applicants amendments to the claims have necessitated a new grounds of rejection, therefore **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

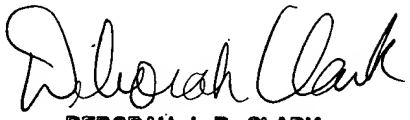
however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732. The examiner can normally be reached on Monday through Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached on (703) 305-6608. The fax number for group 1600 is (703)308-4724.

An inquiry of a general nature or relating to the status of the application should be directed to Kay Pickney whose telephone number is (703) 305-3553.

Joseph T. Woitach



DEBORAH J. R. CLARK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600